Guidance for Industry

Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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OGD

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GUIDANCE FOR INDUSTRY[1]

Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to document the Office of Generic Drugs' (OGD's) policy regarding the determination of major, minor, and telephone amendments to original *and supplemental* abbreviated new drug applications (ANDAs).[2] The guidance was originally entitled *Major, Minor, FAX, and Telephone Amendments to Original Abbreviated New Drug Applications* (revised May 2000). This guidance is a revision of the May 2000 guidance. Revision 2 of the guidance (1) deletes the FAX amendment designation, which was found to be unnecessary, (2) now applies to supplemental applications as well, and (3) changes the criteria for determining the type of amendment. The changes in criteria should result in more amendments being categorized as *minor* and fewer as *major*. A minor amendment request (generally reviewed within 30 to 60 days) has a higher priority than a major amendment. Since the review of a minor amendment takes place sooner than a major amendment after the original review, there is not a long break in the review process for a minor amendment. The response to a major amendment request, however, goes into the 180-day queue. This process causes a greater time lapse from when the original review was done and results in reviewers having to refamiliarize themselves with the application. It is expected that the new policy will help in moving applications through the approval process more quickly than under the previous policy. Thus the total time for approval of ANDAs will be reduced.

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[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER).

[2] This includes revision and clarification of the policy stated in Policy and Procedure Guide (PPG) 38-93, "Restatement of the Office of Generic Drugs' 'First-In, First-Reviewed' Policy and Modification of the Exceptions to the Policy Regarding Minor Amendments," relating to original ANDAs and the policy stated in the guidance to industry *Major, Minor, FAX and Telephone Amendments to Original Abbreviated New Drug Applications*.

II. POLICY

A. How does the Office of Generic Drugs classify amendments?

Generally, the considerations used to categorize amendments requested by OGD are determined by the nature of the chemistry, manufacturing, and controls (CMC), microbiology, labeling, and/or bioequivalence deficiencies.

OGD classifies amendment requests to ANDAs as major, minor, or telephone. Major amendments have the same review priority as original, unreviewed ANDAs and are reviewed in accordance with OGD's first in-first reviewed procedure. Minor amendments have a higher priority than major amendments because they often mean an application is close to approval and should, therefore, be given priority. The issuance of major or minor amendment requests stops the review clock while the applicant addresses the deficiencies noted by OGD, but telephone amendment requests do not stop the clock unless the applicant does not respond within the specified time. Telephone amendments represent the reviewer's highest priority work assignments. Minor amendments are reviewed when the reviewer completes his or her current assignment.

B. When is an amendment classified as *major*?

Responses to the following examples of deficiencies would result in a major amendment. This should not be considered an all-inclusive listing.

1. Manufacture of a new batch of drug product (with supporting information) for any reason; for example:

    - Composition change or reformulation
    - Change in the source of a drug substance
    - Change in manufacturing site
    - Need for a new bioequivalence study (21 CFR 320.21)
    - New in vitro study for a specific product (e.g., metered dose inhalers)
    - Change in major manufacturing process
    - New strength of the product
    - Unacceptable impurities or impurity levels (21 CFR 314.94(a)(9))
    - Unacceptable excipients found during the review (21 CFR 314.94(a)(9))
    - Failed stability data
    - Change in the container-closure system (other than solid oral dosage forms)

2. New bioequivalence study (21 CFR 320.21) that is not related to manufacture of a new batch of the drug product

3. New analytical methods and full validation data (21 CFR 314.94(a)(9))

Any other circumstances that might be considered to be a major amendment should get division level concurrence, including an assessment that the application is of such overall poor quality that substantive review is not possible.

Many of the deficiencies that would be categorized as a major amendment for chemistry would also pertain to the sterility assurance and/or microbiology review (i.e., change in facility or container-closure system). Generally, the microbiology review would not affect the designation determined through the CMC review. However, in rare instances, the sterility assurance and/or microbiology reviews, rather than chemistry, may determine the major amendment designation. This could occur, for example, when extensive validation work is necessary (21 CFR 314.94(a)(9)).

C. When is an amendment classified as minor?

Except for those amendments that are classified as *major* or *telephone*, amendments will be designated as *minor*. Minor amendments often consist of deficiencies that are outside the control of the applicant or deficiencies that are more easily addressed than those in a major amendment. Though most amendments will likely be *minor*, some examples include, but are not limited to:

1. Deficiencies in the drug master file (DMF)

2. Problems regarding good manufacturing practices (GMPs)

3. Incomplete dissolution data

4. Labeling deficiencies that have not been adequately addressed

Sterility assurance and/or microbiology issues that would likely take less than a full day to review would generally fall into the minor amendment category. However, as stated previously, the microbiology designation is determined by the chemistry review.

D. When is an amendment classified as a telephone amendment?[3]

If an amendment would otherwise be classified as *minor*, but the deficiencies are of a limited number or complexity, it can be classified as a telephone amendment at the discretion of the reviewer's team leader. Should this determination occur with the first review cycle of a new application, the division director's or the deputy division director's concurrence will be sought.

The applicant should provide a complete and satisfactory response within 10 calendar days of the call. Such deficiencies include:

1. Clarification of data already submitted

2. Request for a postapproval commitment

3. Final resolution of technical issues, such as finalization of specifications

To expedite the review, telephone amendments can also be requested during the final division or office level administrative review of an ANDA, immediately before tentative or final approval.

III. REVIEW CONSIDERATIONS

A. What are the timeframes for handling amendments?

OGD attempts to review major amendments within 180 days and to review minor amendments within 30 to 60 days. However, not all minor amendments can be reviewed within 60 days. The response to a telephone amendment is reviewed upon receipt.

B. When is an amendment redesignated?

There could be situations during the review of an ANDA that result in the redesignation of an amendment and consequently the status of the ANDA. For example, the chemistry review and the microbiology review of an ANDA can be completed in different timeframes. If the chemistry review is completed first and it is appropriate, OGD will issue a request for a minor amendment response to the deficiencies. If the microbiology review subsequently reveals major deficiencies, these will be communicated to the applicant as a request for a major amendment response. This action will also change the chemistry response to a major amendment.

In some cases, the results of a bioequivalence or labeling review will result in the redesignation of an amendment. For example, if an ANDA is in minor status for chemistry

[3] OGD will accept only hard copies (2) of major and minor amendments for review (21 CFR 314.94). However, OGD will review responses to telephone amendments transmitted by facsimile provided the applicant also submits hard copies (2).

and it is subsequently determined that an in vivo bioequivalence study fails, a redesignation to major will occur. Redesignation to a minor amendment might also occur when a chemistry or microbiology telephone amendment request has not been responded to within 10 days of OGD's request.

C. What is the process for classifying an amendment?

Reviewers will conduct their reviews according to OGD policies. The reviewer makes the initial recommendation to the team leader regarding classification of the amendment to be requested. The team leader will conduct the secondary review and concur with the amendment classification, if appropriate. Division directors (or deputies) will complete any tertiary reviews indicated. If an applicant requests reclassification of an amendment, the director or deputy will review that request. Applicants should respond to all requests for amendments on time and ensure that two hard copies are submitted (21 CFR 314.94) of any material communicated to OGD by facsimile or telephone.

Labeling reviewers will transmit labeling deficiencies directly to the applicant via facsimile in the absence of any CMC, microbiology, or bioequivalence deficiencies, or in the event the labeling review is completed after the remaining deficiencies have been communicated to the applicant. Unless otherwise specified, labeling deficiencies will be issued by facsimile.